Recovery from ICU acquired weakness, don't forget the respiratory muscles!

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Skeletal muscle dysfunction acquired during critical illness (ICU acquired weakness, ICUAW) plays a pivotal role in clinical outcomes such as weaning, ICU length of stay, hospital length of stay, physical function and mortality (1, 2). ICUAW is a common complication of critical illness with a complex aetiology (3), affecting both limb muscles as well as respiratory muscles. The decline in muscle mass is approximately 2-4% per day in the first week of ICU stay (4, 5). Loss of limb muscle mass is more pronounced in patients with multiple organ failure (4), while a rapid decline in diaphragm muscle strength and thickness is associated with sepsis (6) and low diaphragm contractile activity (5). Strategies to prevent or treat ICUAW are scarce and mostly focused on the treatment or reduction of risk factors associated with ICUAW (sepsis, hyperglycaemia, catabolism, neuromuscular blockers and corticosteroids) (3). In addition, immobility and inactivity contributes considerably to muscle atrophy: 'mechanical silencing' has been identified as an important contributor to the loss of contractile properties (7). Therefore, reversing inactivity of the muscle should have the potential to prevent, reverse or ameliorate muscle wasting.

The focus of rehabilitation in critically ill patients is on the prevention and treatment of ICUAW, oftentimes specifically targeting lower limb muscle function. Early mobilisation, transferring patients from the bed to the chair, weight bearing, walking, bed cycling, and neuromuscular electrical stimulation are the most common modalities successfully applied to ameliorate limb muscle weakness and functional status (8). It is unclear as to why the respiratory muscles are only very rarely addressed in these programs. Respiratory muscle dysfunction in mechanically ventilated patients is observed in 80% of patients with ICUAW (9). Goligher and colleagues documented that a lower contractile activity of the diaphragm during mechanical ventilation was associated with further reduction of diaphragm thickness (5). This observation supports the idea that well-balanced intermittent loading of the respiratory muscles during the process of mechanical ventilation might be beneficial to

prevent or ameliorate muscle atrophy. Indeed, modalities inducing (intermittent) loading of the respiratory muscles such as spontaneous breathing trials and early mobilisation have been shown to increase muscle strength (10) and to shorten the duration of mechanical ventilation (11), respectively.

However, 15-20% of patients fails liberation from mechanical ventilation(12). Inadequate ventilatory drive, increased work of breathing, and weakness of the respiratory muscles are likely to contribute to weaning failure (13). The inability to breathe spontaneously relates to an imbalance between *load on* the respiratory muscles and the *capacity of* the respiratory muscles (14). Indeed, high rates of respiratory muscle effort (ratio of workload and muscle capacity (P_I/P_{Imax})) are a major cause of ventilator dependency and predict the outcome of successful weaning (15). In patients at risk for ventilatory failure following extubation, *unloading* of the respiratory muscles with non-invasive ventilation has been shown successful in facilitating discontinuation of invasive mechanical ventilation (16). Surprisingly, little attention has been given to specific interventions to enhance strength and endurance of the respiratory muscles. Indeed, daily intermittent inspiratory loading with 6 to 8 contractions repeated in 3 to 4 series at moderate to high intensity was safe, improved inspiratory muscle strength and weaning success in patients with difficult weaning (17). One of the challenges of these studies is that patients who might benefit from the intervention are oftentimes not sufficiently able to participate in the training sessions.

Given the difficulties of inspiratory muscle training (IMT) during mechanical ventilation as well as the fact that weakness persists after successful extubation (18), targeted training approaches following successful extubation might be warranted. This question was adequately addressed in the current issue of *Thorax* by Bissett and colleagues. The authors provided IMT for 2 weeks in patients who were successfully weaned from mechanical ventilation. This approach might boost the rehabilitation allowing better coping with the ventilatory demands during walking, cycling, activities of daily living, improve quality of life and reduce dyspnea. As expected, PImax improved significantly in the intervention group (17% pred vs 6% pred in the control group), but no improvements in inspiratory muscle endurance, physical function and dyspnoea were observed. Disappointing at first glance, but several reasons could have been involved in the lack of transfer effects to exercise performance and dyspnea. First, 2 weeks of training may be too short to improve exercise performance and dyspnoea. To obtain these effects, a rehabilitation program combining

limb muscle training and respiratory muscle training is probably warranted. Since no data were collected on the progress of training intensity during the 2 weeks, it is unknown how patients tolerated the increased training intensity. Improvements in PImax varied substantially and increased specifically in patients with relatively preserved PImax, while patients with very low PImax showed modest improvements. This might be related to the fact that a low training intensity could not be adequately set. The minimal inspiratory resistance at the Threshold^{R} device is 9 cm H_20 and this might have been too high for very weak patients. In general, threshold loading might be less optimal compared to (electronic) tapered flow resistive loading (19). The latter type of inspiratory muscle loading starts at very low intensity (4cm H_2O). In addition, the attenuating resistance over the inspiratory cycle allows training with a larger tidal volume, higher power per breath and less dyspnoea (19). In COPD patients this device has been shown more effective in improving inspiratory muscle strength and endurance (19). The lack of improvement in muscle endurance in the study of Brissett et al. might also be related to the incremental loading protocol that was applied. In general, a constant load protocol is a more sensitive measure and might reflect better endurance capacity than the incremental loading protocol. Moreover, in the present study patients were not specifically selected with inspiratory muscle weakness, the considered target population for such interventions. On average patients had reduced PImax, but several patients had at the time of enrolment (near) normal respiratory muscle strength. These patients are probably not appropriate candidates for respiratory muscle training interventions. Furthermore, it is questionable whether the training device used by the authors was capable of providing a sufficiently high training stimulus for these patients with near normal respiratory muscle strength.

Finally, the mortality in the experimental group (12%) was anticipated in the design of the study (12,5%), but the control group had a (borderline statistically significant) lower mortality. This unexpected difference in mortality was not related to the IMT sessions nor to respiratory complications. The authors suggested that the heterogeneity and the size of the study group might explain this finding. The higher mortality in the IMT group is in contrast with findings reported in a recent meta-analysis on the effects of IMT to facilitate liberation from mechanical ventilation. The authors reported a slightly *higher*, but not statistically significant, likelihood of *survival* in the IMT group when pooling data from four studies

(n=242; relative risk [95% CI] of survival: 1.04 [0.96 - 1.13]) (17). Weighted mortality rates were 6.4% in the intervention group and 10.3% in the control group.

Considering the promising results of the study of Bissett and colleagues and the emerging role of ICUAW, including respiratory muscle weakness, future studies are warranted. Since *unsupervised* homebased post-ICU rehabilitation has been unsuccessful (20), a *supervised* rehabilitation program including IMT should be investigated in patients with inspiratory muscle weakness. The outcomes of these studies should specifically focus, in addition to respiratory and limb muscle function, on dyspnea, respiratory infections, hospital and ICU stay, hospital and ICU readmission, exercise capacity, functional status, and quality of life.

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